Kidney International, Vol. 7 (1975), p. 103–110

Factors influencing sodium and water excretion in uremic man

BETTY P. Y. YEH, DAVID J. TOMKO, WILLIAM K. STACY, EDWARD S. BEAR, HALCOTT T. HADEN and WILLIAM F. FALLS, JR.

Medical Service, Veterans Administration Hospital and Department of Medicine, Medical College of Virginia, Health Sciences Division, Virginia Commonwealth University, Richmond, Virginia

Factors influencing sodium and water excretion in uremic man. Urinary excretion of sodium and water was investigated in patients with chronic end-stage renal disease before and after three different experimental manipulations: reduction in urea solute load by dialysis while extracellular fluid volume (ECFV) was maintained, dialysis without alteration in urea solute load or ECFV and reduction in ECFV without alteration in urea solute load. Sodium and water excretion significantly declined in association with a reduction in both urea solute load and ECFV, but not during a dialysis when reduction on both of these indexes was prevented. The excretory changes occurred in the absence of any alteration in creatinine clearance. The studies suggest that both solute load and the degree of extracellular fluid volume expansion contribute independently to the rate of sodium and water excretion in chronic renal disease. It is concluded that in any given patient the overall excretion of sodium and water is directly influenced by a number of factors including the solute load, the degree of ECFV and the glomerular filtration rate.

Facteurs qui influencent l'excrétion d'eau et de sodium chez l'homme urémique. L'excrétion urinaire de sodium et d'eau a été étudiée chez des malades atteints de néphropathie chronique au stade terminal avant et après trois manoeuvres expérimentales: réduction de la masse d'urée par dialyse cependant que le volume extracellulaire (ECVF) était maintenu, dialyse sans modification de la masse d'urée ou d'ECVF, réduction d'ECVF sans modification de la masse d'urée. L'excrétion d'eau et de sodium diminue significativement lors de la réduction simultanée de la masse d'urée et d'ECVF, mais n'est pas modifiée per la dialyse quand les deux paramètres ci-dessus sont maintenus constants. Les modifications excrétoires surviennent en l'absence de tout changement de la clearance de la créatinine. Ces travaux suggèrent qu'à la fois la charge de soluté et le degré d'expansion extracellulaire contribuent indépendamment aux débits d'excrétion de sodium et d'eau dans l'insuffisance rénale chronique. Il est conclu que chez un malade donné, l'excrétion globale d'eau et de sodium est directement influencée par divers facteurs dont la charge de substances dissoutes, le degré d'expansion du volume extracellulaire et le débit de filtration glomérulaire.

Sodium and water excretion in normal animals and man is finely controlled by the complex interplay of various hormonal, hemodynamic and physio-chemical factors [1]. Despite the loss of a major portion of the functioning nephron mass, uremic subjects largely maintain the ability to modulate sodium excretion in relation to intake [2], thus suggesting at least partial retention of some control mechanisms.

A complete understanding of the mechanisms of adaptation which allow the residual nephrons of the damaged kidney to handle sodium loads has not yet been attained. Disagreement exists among investigators about the relative importance of the several factors which are suspected of being operative in controlling sodium excretion in uremia. Some investigators [3–5] feel that the osmotic effect of an increased solute load, composed primarily of urea and other nonreabsorbable substances, plays a major role in enhancing the excretion of sodium and water. Others [6–8] have relegated this mechanism to a position of minimal importance and instead relate the excretory changes to some factor inherent in the uremic state which enhances sodium and water excretion. A circulating inhibitor to sodium reabsorption has been recently identified in uremic serum [9]. However, whether this factor is generated by the uremic state, *per se*, or as a response to the extracellular fluid volume (ECFV) expansion which usually accompanies renal failure is uncertain [10]. Furthermore, it is unclear whether the well recognized effect of ECFV expansion is mediated primarily through an inhibition of proximal or distal tubular reabsorptive processes [6, 8, 11] or via renal hyperperfusion and an increased glomerular filtration rate (GFR) secondary to blood pressure elevation [12]

The present study was undertaken to dissociate and examine separately the effects of solute load and ECFV expansion on sodium and water excretion in a

Received for publication June 29, 1973;
and in revised form August 14, 1974.

group of patients with chronic renal failure. In the process of examining the influence of ECFV alone, some observations were also made on the relation of this index to blood pressure changes.

Methods

Patients selected. Twenty-eight patients with chronic end-stage renal failure of varying etiologies (Table 1) were studied at the McGuire Veterans Administration Hospital. Twenty-seven of the patients were either enrolled or being evaluated for acceptance into a repetitive hemodialysis program when they entered the study. One was receiving repetitive peritoneal dialysis. Informed consent was obtained from each patient prior to the institution of the investigation. All patients were receiving dietary protein restriction (40 to 80 g/24 hr), aluminum hydroxide gels, vitamin supplements and in most cases modest dietary sodium restriction (44 to 125 mEq/24 hr). None of the patients were taking diuretics at the time of the study, but several were undergoing treatment for hypertension with alpha-methyldopa (Aldomet). None showed clinical evidence of pulmonary congestion. Most of the hemodialysis patients were considered candidates for renal transplantation and demonstrated complete bladder emptying by voiding cystography. The peritoneal dialysis patient showed adequate bladder function by having a negligible residual urine volume after spontaneous voiding. One paraplegic, hemodialysis patient had urine collected from a nephrostomy tube and an indwelling Foley catheter.

Studies performed. Measurements of blood pressure, body wt, plasma urea nitrogen concentration (PUN), plasma osmolality (P_{Osm}), serum electrolyte concentrations, urine osmolality and ECFV (^{35}S space) were made at several points in the course of dialysis as outlined in the following. Because of variability in the volume of urine excreted, collection periods varied from 1 to 24 hr, but all were accurately timed and a plasma specimen was obtained at approximately the midpoint of each period for use in clearance calculations. No meals were withheld during the initial or later studies and the patients were allowed to have fluids *ad lib* but were not water-loaded. It was assumed that urinary excretion in these patients with severe

Table 1. Clinical information concerning study patients

Patient No.	Age *yr*	Creatinine clearance *ml/min*	Blood pressure *mm Hg*	Cause of renal disease
1	35	2.8	120/80	Pyelonephritis, congenital anomaly[a]
2	45	7.5	110/70	Polycystic
3	39	8.9	135/70	Chronic glomerulonephritis[a]
4	50	8.5	170/100	Nephrosclerosis[a]
5	34	2.5	160/90	Nephrosclerosis[a]
6	48	6.2	210/120	Nephrosclerosis
7	48	8.7	160/90	Chronic pyelonephritis, amyloidosis[a]
8	32	8.0	120/90	Polycystic
9	35	4.2	200/140	Nephrosclerosis[a]
10	38	9.4	134/80	Polycystic
11	53	3.9	160/60	Polycystic
12	50	3.7	120/80	Polycystic[a]
13	42	2.8	160/80	Chronic glomerulonephritis
14	35	0.7	200/130	Nephrosclerosis[a]
15	55	7.6	150/90	Chronic glomerulonephritis
16	50	12.6	200/110	Nephrosclerosis[a]
17	56	4.9	150/90	Polycystic
18	50	6.8	130/90	Polycystic[a]
19	51	4.6	130/90	Chronic glomerulonephritis[a]
20	36	2.7	130/80	Chronic glomerulonephritis[a]
21	59	1.6	185/100	Chronic glomerulonephritis
22	25	1.0	200/120	Chronic glomerulonephritis
23	47	4.5	140/90	Chronic glomerulonephritis
24	49	3.9	140/90	Chronic glomerulonephritis
25	48	5.5	122/70	Chronic glomerulonephritis
26	50	7.4	182/90	Chronic glomerulonephritis[a]
27	21	2.4	110/70	Chronic glomerulonephritis
28	50	2.6	180/90	Chronic glomerulonephritis[a]
Mean	43.9	5.2		

[a] Diagnosis confirmed by histologic evaluation.

renal insufficiency would not be significantly influenced by mild variations in fluid intake.

Plan of investigation. 1) Group I: Evaluation of the influence of solute load. In nine patients with minimal evidence of clinical volume expansion, the indexes already mentioned herein were initially measured prior to any dialysis when the patient was assumed to have a high load of retained solutes. After baseline data had been obtained, the patients underwent a hemodialysis during which fluids were given i.v. and orally in amounts calculated to maintain body wt constant. This was done in an effort to vary solute load by dialysis while maintaining ECFV constant. Repeat ^{35}S space, creatinine clearance and electrolyte excretion were then measured after dialysis. It was discovered early that ^{35}S space measurements decreased in most patients despite maintenance of body wt, and that ECFV could be maintained only by giving sufficient fluids to increase body wt by an average of 0.4 kg in these individuals. Therefore, those patients with a postdialytic reduction in ^{35}S space underwent further dialysis during which more fluid was administered until the postdialysis ECFV was equal to or slightly greater than the original determinations. Four patients who had received prior dialysis were initially studied immediately after dialysis and again several days later when the solute load had reattained a high level but ECFV was still low because of careful fluid and sodium restriction. In this manner urinary excretion was examined in 13 patients at two greatly different solute loads but relatively comparable levels of ECFV.

2) Group II: Evaluation of the influence of dialysis alone. Because of the possibility that any urinary excretory change noted in group I patients might be related to the dialysis itself rather than to alteration in the solute load, seven patients were subjected to dialysis against a bath to which urea was added in an amount calculated to maintain the bath concentration the same as plasma. During dialysis in this group, fluid intake was also carefully controlled to avoid either a significant increase or reduction in the ECFV.

3) Group III: Evaluation of the influence of the level of ECFV—its relation to blood pressure and GFR. In 14 patients (4 of whom were also included in group I) determinations of blood pressure, ^{35}S space, creatinine clearance and electrolyte excretion were made at two different points in time; once when the ECFV was high, and again when it was lower but the level of azotemia was essentially the same.

Dialysis methods. Hemodialyses were performed for four to eight hours using a Milton-Roy central dialysate delivery system with a variety of dialyzers including the modified Kiil, Dow hollow fiber, Gambro-Lundia and Travenol Ultra-flow 145 coil in groups I and III. All dialyses in group II were performed with a single-pass recirculating system using a Travenol RSP dialyzer and a Travenol Ultra-flow 145 coil. It was assumed for the purposes of this study that the function of all of the dialyzers was qualitatively similar.

Analytical and statistical methods. ^{35}S space was determined by a modification of the method of Walser, Seldin and Grollman [13]. Plasma was collected at 30, 45, 60 and 90 min after injection of 60 to 90 μCi of ^{35}S. Isotope counting was done in a liquid scintillation counter (Nuclear-Chicago) and counts at zero time calculated by the method of least squares on a computer (IBM 370). ^{35}S space was then determined from the following formula:

$$\text{Volume of distribution} = \frac{\text{Counts per minute of standard} \times \text{dilution} \times 0.90}{\text{Counts per minute per ml of plasma water}}.$$

The factor of 0.90 was used as the Donnan factor for the sulfate ion. Plasma and urine creatinine, urea nitrogen and electrolyte determinations were made by methods routine to this laboratory [14]. Blood pressure was measured with a sphygmomanometer and mean pressure calculated as diastolic pressure plus one-third pulse pressure. The data from the control and experimental period were compared in each group and subjected to statistical analysis by a standard paired *t* test programmed on a computer (IBM 370).

Results

Clinical state of patients. Table 1 provides clinical information about the patients involved in the study. It is worthy of note that the etiologic processes in this group of patients encompassed a wide spectrum of end-stage renal disease and included processes which are considered to be primarily destructive to both the glomerular and tubular portions of the nephron. Diagnosis was made in most cases by evaluation of the clinical and roentgenographic picture and was confirmed in 14 by pathologic evaluation at biopsy, nephrectomy or necropsy. GFR as indicated by the creatinine clearance varied from 0.7 to 12.6 ml/min with a mean of 5.2 ml/min. All patients had evidence of a uremic syndrome and required dialysis therapy. Blood pressure varied from normal to high levels but was highest in those patients with malignant nephrosclerosis.

Evaluation of the influence of solute load on urinary excretion. The data from group I patients (Table 2, Fig. 1) show that dialysis produced a significant reduction in solute load as reflected by the decline in mean PUN from 115 to 62 mg/100 ml, P_{Osm} from 330 to 302 mOsm/kg, urine osmotic excretion ($U_{Osm}V$)

Table 2. Comparison of mean ± SD baseline and experimental values in group I patients (solute load reduced; ECFV maintained in the experimental period)

	ECFV *ml*	Urine volume *ml/min*	Creatinine clearance *ml/min*	Plasma urea nitrogen *mg/100 ml*	Plasma osmolality *mOsm/kg*	Plasma sodium *mEq/liter*	Sodium excretion *μEq/min*	Osmotic excretion *μOsm/min*	Urea nitrogen excretion *mg/min*	Fractional reabsorption of sodium %	Mean blood pressure *mm Hg*
High solute load	13038 ±2454	1.04 ±0.47	6.1 ±2.5	115 ±40	330 ±17	137 ±4	50.2 ±28.2	286 ±119	3.7 ±1.9	93.2 ±4.3	116 ±28
Low solute load	13495 ±2506	0.82 ±0.39	6.4 ±2.5	62 ±32	302 ±19	135 ±5	29.9 ±19.1	168 ±80	1.8 ±0.8	96.1 ±2.5	119 ±29
P	<0.02	<0.02	NS	<0.001	<0.001	NS	<0.01	<0.001	<0.001	<0.01	NS

from 286 to 168 μOsm/min and urine urea nitrogen excretion ($U_{Urea}V$) from 3.7 to 1.8 mg/min. ECVF was slightly increased ($P < 0.02$) by the fluids administered during dialysis. Mean creatinine clearance remained at essentially predialysis levels in association with the maintenance of ECFV. Plasma sodium concentration and blood pressure measurements were not significantly altered by dialysis. Fig. 1 illustrates the changes in sodium excretion ($U_{Na}V$) and fractional reabsorption of sodium in each patient. Mean values for these indexes as seen in Table 2 showed a significant fall in urine volume (UV) from 1.04 to 0.82 ml/min ($P < 0.02$) and sodium excretion ($U_{Na}V$) from 50.2 to 29.9 μEq/min ($P < 0.01$). The reduction in sodium excretion was a direct result of enhanced tubular reabsorption as indicated by the increased fractional reabsorption of sodium from 93.3 to 96.0% in the face of maintained creatinine clearance. These excretory alterations become even more striking when it is realized that ECFV actually rose slightly, a trend that might have tended to offset changes related to the reduction in solute load. These data, thus, indicate that the fall in water and sodium excretion following dialysis correlates closely with the reduction in solute load.

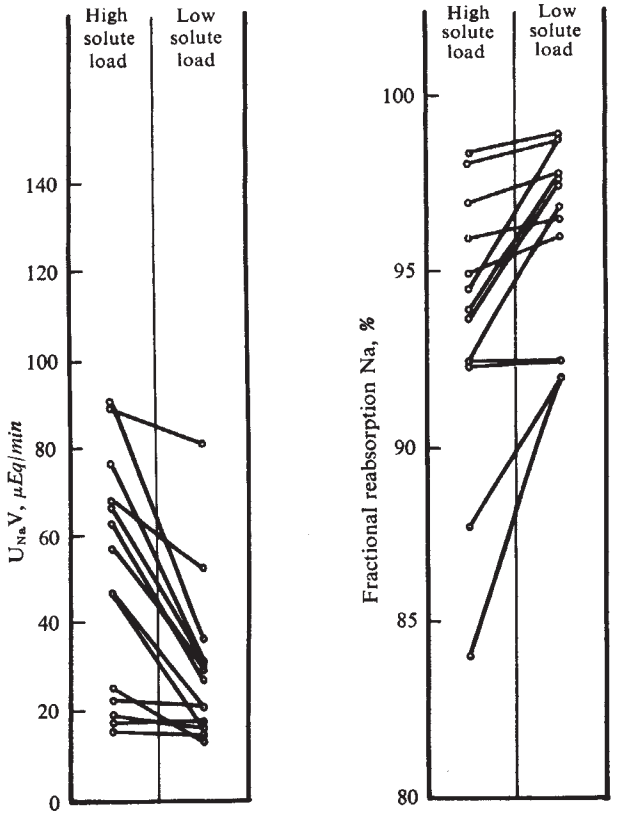

Fig. 1. *Urine Na excretion ($U_{Na}V$) and fractional reabsorption of Na in group I patients.*

Factors other than solute load must also have been altered by the dialytic process. Therefore, in order to maintain constancy of urea, the major osmotically active solute, group II patients were evaluated before and after dialysis against a high urea bath. Fig. 2 illustrates the changes in $U_{Na}V$ and fractional reabsorption of sodium for individual patients. Table 3 shows that with maintenance of the solute load by adding urea to the dialysis bath, there was no significant change in mean V, $U_{Na}V$, $U_{Osm}V$, $U_{Urea}V$, C_{creat}, PUN, fractional reabsorption of sodium or BP during the dialysis period. A slight but significant reduction in P_{Osm} occurred, probably reflecting the dialysis of other nonurea solutes; and a slight fall in P_{Na} was seen as a result of dialysis against a slightly lower concentration of sodium in the bath. Thus, consideration of the data from both groups I and II suggests that the reduction in urine volume and sodium excretion which follows dialysis in the ECFV-maintained patient is a consequence of the change in solute load *per se* rather than of some other dialysis-induced perturbation.

Evaluation of the influence of ECFV on urinary excretion. Table 4 and Fig. 3 display the data from group III patients in whom solute load remained constant as ECFV decreased. Significant reductions in V (0.98 to 0.73 ml/min, $P < 0.01$) and $U_{Na}V$ (50.0 to

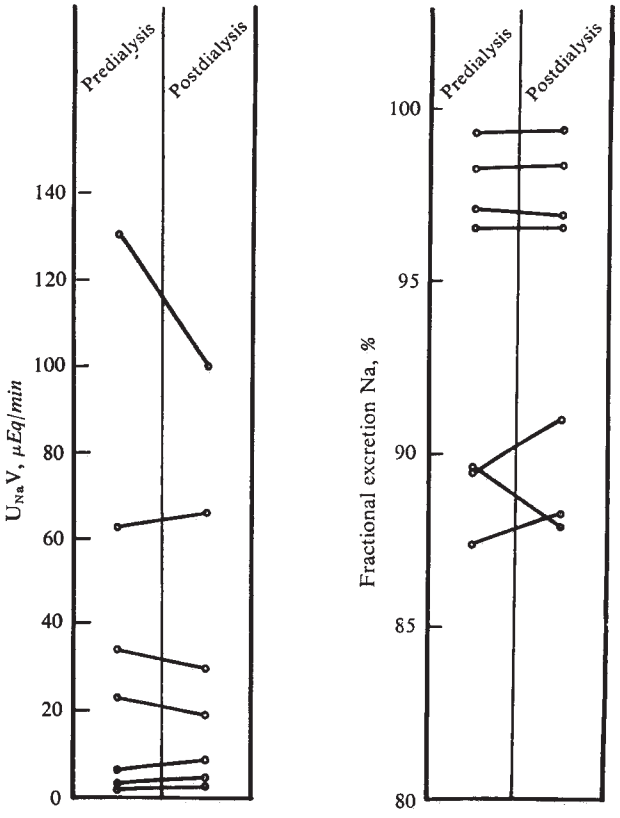

Fig. 2. *Urine excretion ($U_{Na}V$) and fractional reabsorption of Na in group II patients.*

31.5 μEq/min, $P<0.001$) and an increase in fractional reabsorption of sodium from 93.6% to 95.5% ($P<0.01$) occurred in conjunction with the fall in ECFV. Despite the major change in mean ECFV from 16,344 to 14,054 ml, there was no significant alteration in GFR (C_{creat}). This lack of change was undoubtedly related to the fact that the ECFV remained relatively expanded [13] even though it was reduced from an even higher level in most patients. The reduction in ECFV was associated with a slight reduction in mean blood pressure from 117 ± 24 to 109 ± 21 mm Hg ($P<0.01$), however. These findings are compatible with the concept that when the influence of differing solute loads is removed, sodium and water excretion is influenced directly by the level of ECFV, being greater with a more expanded ECFV. Additionally, since the reduction in sodium and water excretion occurred in the absence of a change in GFR, the increased fractional reabsorption of sodium must have been produced by an enhancement of the intrinsic reabsorptive capacity of the tubules.

Discussion

Despite the loss of a major portion of the nephron mass, many patients with chronic end-stage renal disease continue to excrete sufficient sodium and water to balance the daily intake [2, 6, 15, 16]. This ability of

Table 3. Comparison of mean ± SD baseline and experimental values in group II patients (dialysis; solute load maintained constant in experimental period with a high urea bath)

	ECFV *ml*	Urine volume *ml/min*	Creatinine clearance *ml/min*	Plasma urea nitrogen *mg/100 ml*	Plasma osmolality *mOsm/kg*	Plasma sodium *mEq/liter*	Sodium excretion *μEq/min*	Osmotic excretion *μOsm/min*	Urea nitrogen excretion *mg/min*	Fractional reabsorption of sodium %	Mean blood pressure *mm Hg*
Baseline	16034 ±2158	0.62 ±0.52	3.9 ±2.1	118 ±49	336 ±22	135 ±4	38.0 ±46.4	201 ±170	2.4 ±1.9	94.0 ±4.9	107 ±16
After dialysis	16034 ±1983	0.59 ±0.44	3.9 ±1.8	124 ±45	331 ±21	132 ±3	32.7 ±37.0	185 ±145	2.4 ±2.0	94.2 ±4.9	110 ±25
P	NS	NS	NS	NS	<0.01	<0.05	NS	NS	NS	NS	NS

Table 4. Comparison of mean ± SD baseline and experimental values in group III patients (solute load maintained, ECFV reduced in the experimental period)

	ECFV *ml*	Urine volume *ml/min*	Creatinine clearance *ml/min*	Plasma urea nitrogen *mg/100 ml*	Sodium excretion *μEq/min*	Fractional reabsorption of sodium %	Plasma sodium *mEq/liter*	Mean blood pressure *mm Hg*
High ECFV	16344 ±4565	0.98 ±0.60	5.6 ±3.3	70.1 ±26.9	50.0 ±34.2	93.6 ±3.0	135 ±7	117 ±24
Reduced ECFV	14054 ±3569	0.73 ±0.47	5.4 ±3.5	73.9 ±28.9	31.5 ±28.3	95.5 ±2.4	134 ±7	109 ±21
P	<0.001	<0.01	NS	NS	<0.001	<0.01	NS	<0.01

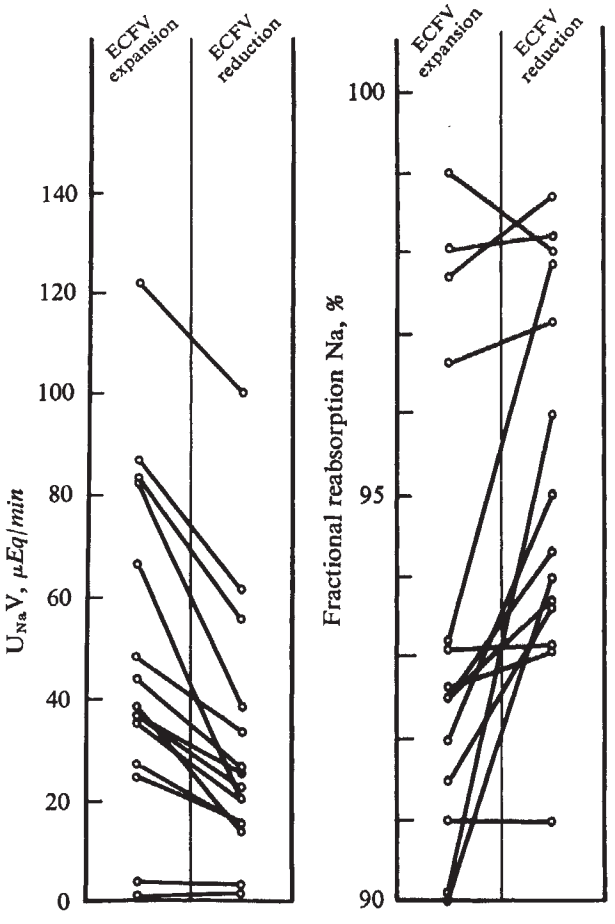

Fig. 3. *Urine Na excretion ($U_{Na}V$) and fractional reabsorption of Na in group III patients.*

the damaged kidney to maintain fluid and electrolyte homeostasis is dependent on an adaptive reduction in the fractional reabsorption of filtrate by the residual nephrons. The origin of such an adaptive change is incompletely defined, but by analogy to the normal state of sodium and water homeostasis [1, 10] is likely to be modulated by several interacting factors rather than be explained by a single mechanism [9].

Initially it was suggested that the reabsorptive adaptation was the result of a urea, solute diuresis [2, 17, 18]. Support for this concept was found by observation of the diuresis in animals [19] and humans [16] subjected to urea infusions; by the micropuncture studies of Hayslett, Kashgarian and Epstein in uremic rats [4]; and by the demonstration of Coleman et al [3] that sodium wasting in chronic renal disease is related to an inhibition of the maximal concentration gradient for sodium in the distal tubule by an increase in osmotically active, nonreabsorbable solute in that portion of the nephron.

Skepticism about the role of a urea diuresis in enhancing sodium and water excretion in chronic renal failure has been raised because of two recent developments: *1*) reevaluation of the techniques used in early studies of urea diuresis has indicated contamination by an element of ECFV expansion [20]; *2*) suggestive evidence for a factor or factors which may directly inhibit tubular sodium transport has been found in the uremic state [9]. Results from the former studies do not exclude urea, osmotic diuresis from a partial or contributory role, however; and the influence of the uremic state has not been clearly dissociated from changes in the degree of ECFV expansion in the latter investigations (*vide infra*) [6, 10, 11].

ECFV expansion frequently accompanies chronic renal failure as attested by the high ECFV levels observed in many of the patients in this study and by measurement of fluid spaces by others [21, 22]. Expansion of the ECFV may enhance sodium excretion by several different mechanisms: *1*) by elevation of systemic blood pressure [12]; *2*) by inhibition of endogenous aldosterone secretion, although current evidence suggests that this may seldom be the case in patients with severe renal insufficiency [5, 6, 11]; and *3*) perhaps most important, by release of a circulating humoral factor which acts to inhibit reabsorptive processes in the proximal tubule [6, 9, 10] in the expanded and uremic state.

The present study was designed to dissociate the influence of ECFV expansion and solute load on sodium and water excretion in uremic patients and to determine the role played by each independently. The data indicate that in men with chronic renal insufficiency both solute load and the level of ECFV expansion contribute significantly and separately to the role of sodium and water excretion.

The role of solute load is strongly suggested by consideration of the data from group I and II patients. In group I the PUN and P_{Osm} were reduced by dialysis while ECFV was slightly raised by sodium and fluid administration (Table 2). Sodium and water excretion diminished despite the slight elevation in mean ECFV (Table 2, Fig. 1). A dialysis-induced alteration other than that of osmotic load seemed less likely in view of the fact that a significant change in sodium and water excretion was not observed when a high solute load was maintained by dialysis against a high urea bath (group II) (Table 3, Fig. 2). Thus, the osmotic effect of an increased solute load (primarily urea) can be identified as a major influence tending to enhance sodium excretion in chronic renal insufficiency.

The data in group III patients clearly indicate that at a constant solute load and GFR, more sodium and water was excreted in the expanded state. No definite statement can be made as to the mechanisms whereby ECFV expansion leads to increased excretion, whether

to an inhibition of aldosterone activity or to increased release of a circulating humoral factor, or both. Sodium excretory changes could not be related to alterations in GFR because none were noted during the study. A small but significant reduction in blood pressure was noted, however, in conjunction with the fall in ECFV induced in group III patients. It is possible that this change may have resulted in unmeasured alterations of renal hemodynamics which in turn influence sodium and water reabsorption [23].

The results of the present study in no way preclude the operation of a circulating humoral factor which might act to inhibit renal tubular sodium reabsorption in uremic patients. It is possible that such a factor was present during the studies of group I and II patients but its action was uninfluenced by dialysis. Even if it were influenced by dialysis, however, its effect could have been masked by the wide scatter of the data in group II patients. Since ECFV expansion was present in group II patients both before and after dialysis, it may be that a circulating humoral factor, responsive to volume changes, was present throughout the study. Furthermore, the data in group III patients are entirely compatible with the action of an expansion-induced circulating humoral factor controlled by the level of ECFV expansion.

Overall analysis of the data presented in this investigation strongly suggests that both solute load and the degree of ECFV expansion are of importance in controlling sodium and water excretion in patients with chronic renal failure. This is not meant to imply, however, that these are the only factors which may be operative. There is good evidence to indicate that reduction of ECFV below the expanded range will tend to cause sodium retention because of a concomitant fall in blood pressure with consequent reduction in renal perfusion and GFR [12]. Thus, it would appear that the dramatic reduction in urinary output and sodium excretion experienced by virtually all patients after initiation of dialysis [2, 17, 18] is a manifestation of the conjoint effects of a fall in ECFV, GFR and solute load. Conversely, it would seem reasonable to postulate that the adaptation which allows many uremic subjects to excrete relatively large amounts of sodium prior to dialysis must be related to an elevation of all of the above-mentioned factors acting in concert. Whether or not some other factor related to loss of nephron mass, *per se*, may be operative in the uremic state cannot be ascertained with certainty from this study.

It is apparent that maximal excretion of sodium and water by the patient with chronic renal insufficiency can be attained only at the expense of both marked azotemia and ECFV expansion. Furthermore, a major reduction in ECFV in the patient with chronic renal failure will almost certainly lead to a fall in blood pressure and GFR and, consequently, further reduce sodium excretion. Thus, the clinician can adequately judge a patient's tolerance for sodium and water only in the context of his state of volume expansion and degree of azotemia.

Acknowledgments

This work was funded by the Veterans Administration (MRIS 2737-Project 08). Mrs. Ursula J. Edmonds performed the chemical analyses and Mrs. Marjorie Stephenson assisted with the ^{35}S determinations.

Reprint requests to Dr. W. F. Falls, Jr., Renal Section, Veterans Administration Hospital, Richmond, Virginia 23249, U.S.A.

References

1. DE WARDENER HE: The control of sodium excretion, in *Handbook of Physiology: Section 8: Renal Physiology*, edited by GEIGER SE, Washington DC, American Physiology Society, 1973, pp. 677–720
2. MERRILL JP, HAMPERS CL: Uremia. *N Engl J Med* 282:953–961; 1014–1021, 1970
3. COLEMAN AJ, ARIAS M, CARTER NW, RECTOR FC, SELDIN DW: The mechanism of salt wastage in chronic renal disease. *J Clin Invest* 45:1116–1125, 1966
4. HAYSLETT JP, KASHGARIAN M, EPSTEIN FH: Mechanisms of change in the excretion of sodium per nephron when renal mass is reduced. *J Clin Invest* 48:1002–1006, 1969
5. KLEEMAN CR, OKUN R, HELLER RJ: The renal regulation of sodium and potassium in patients with chronic renal failure (CRF) and the effect of diuretics on the excretion of these ions. *Ann N Y Acad Sci* 139:520–539, 1966
6. BRICKER NS: The control of sodium excretion with normal and reduced nephron populations. *Am J Med* 43:313–321, 1967
7. SCHULTAE RG, SHAPIRO HS, BRICKER NS: Studies on the control of sodium excretion in experimental uremia. *J Clin Invest* 48:869–871, 1969
8. SWALES JD, THURSTON H, POHL JEF: Sodium conservation in chronic renal failure: Studies using oral diazoxide. *Clin Sci* 43:771–778, 1972
9. BRICKER NS, BOURGOIGNIE JJ, KLAHR S: A humoral inhibitor of sodium transport in uremic serum. *Arch Intern Med* 126:860–864, 1970
10. SCHRIER RW, DE WARDENER HE: Tubular reabsorption of sodium ion: Influence of factors other than aldosterone and glomerular filtration rate. *N Engl J Med* 285:1231–1243; 1292–1303, 1971
11. SLATOPOLSKY E, ELKAN IO, WEERTS C, BRICKER NS: Studies on the characteristics of the control system governing sodium excretion in uremic man. *J Clin Invest* 47:521–530, 1968
12. WILKINSON R, LUETSCHER JA, DOWDY AJ, GONZALES OC, NOKES GW: Studies on the mechanism of sodium excretion in uremia. *Clin Sci* 42:711–723, 1972
13. WALSER M, SELDIN DW, GROLLMAN A: An evaluation of radiosulfate for the determination of the volume of extracellular fluid in man and dogs. *J Clin Invest* 32:299–311, 1953

14. FALLS WF JR, STACY WK, BEAR ES, HADEN HT: Dialysis-induced change of extracellular fluid volume in man. *Proc Clin Dialysis Transplant Forum* 2:155–159, 1972
15. PLATT R: Sodium and potassium excretion in chronic renal failure. *Clin Sci* 9–10:367–377, 1950–51
16. MCCANCE RA: The excretion of urea, salts, and water during period of hydropaenia in man. *J Physiol* 104:196–209, 1945
17. MERRILL JP, LEGRAIN M, HOIGNE R: Observations on the role of urea in uremia. *Am J Med* 14:519–520, 1953
18. AOYAMA S, KOLFF WJ: Treatment of renal failure with the disposable artificial kidney. *Am J Med* 23:565–578, 1953
19. ANSLOW WP JR, WESSON LC JR: Effect of sustained graded urea diuresis on water and electrolyte excretion. *Am J Physiol* 180:605–611, 1955
20. KAUKER ML, LASSITER WE, GOTTSCHALK CW: Micropuncture study of effects of urea infusion on tubular reabsorption in the rat. *Am J Physiol* 219:45–50, 1970
21. HAMPERS CL, SKILLMAN JJ, LYONS JH, OLSEN JE, MORRILL JP: A hemodynamic evaluation of bilateral nephrectomy and hemodialysis in hypertensive man. *Circulation* 35:272–288, 1967
22. GRAHAM JA, LAWSON DH, LINTON AL: Muscle biopsy water and electrolyte contents in chronic renal failure. *Clin Sci* 38:583–591, 1970
23. EARLEY LE, SCHRIER RW: Intrarenal control of sodium excretion by hemodynamic and physical factors, in *Handbook of Physiology. Section 8: Renal Physiology*, edited by GEIGER SE, Washington, DC, American Physiology Society, 1973, pp. 721–762